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Original article

Sex-specific associations of maternal birthweight with offspring birthweight in the Omega study

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ABSTRACT

Purpose: We investigated nonlinear and offspring sex–specific associations of maternal birthweight (BW) with offspring BW among participants of the Omega study, a pregnancy cohort.
Methods: Maternal BW was modeled as a continuous variable, linear spline and binary variable indicating low birthweight (LBW; <2500 vs. ≥2500 grams). Offspring BW was modeled as a continuous and binary variable in regression models. Nonlinearity was assessed using likelihood ratio tests (LRTs) in marginal linear spline models.
Results: For every 100-gram increase of maternal BW, offspring BW increased by 22.29 (95% CI: 17.57, 27.02) or 23.41 (95% CI: 6.87, 39.96) grams among mothers with normal BW or born macrosomic, respectively, but not among LBW mothers (β = −8.61 grams; 95% CI: −22.88, 5.65; LRT *P*-value = .0005). For every 100-gram increase in maternal BW, BW of male offspring increased 23.47 (95% CI: 16.75, 30.19) or 25.21 (95% CI: 4.35, 46.07) grams among mothers with normal BW or born macrosomic, respectively, whereas it decreased 31.39 grams (95% CI: −51.63, −11.15) among LBW mothers (LRT *P*-value < .0001). Corresponding increases in BW of female offspring (16–22 grams) did not differ among mothers with LBW, normal BW or macrosomia (LRT *P*-value = .9163).
Conclusions: Maternal and offspring BW associations are evident among normal BW and macrosomic mothers. These associations differ by offspring sex.

Introduction

Birthweight (BW) is an indicator of fetal growth and development [1] which are important determinants of life course health. Low birthweight (LBW), less than 2500 grams, is associated with an increase in risk for morbidity and mortality in infancy [2,3], and chronic diseases in adulthood [4–6]. LBW has a multifactorial origin [7]. Several proximal risk factors including those during or immediately before the pregnancy (e.g., maternal age and prepregnancy body mass index [ppBMI]) have been identified [7,8]. From a life-course perspective, distal risk factors such as mothers' BW, childhood health, and early life socioeconomic position affect later-life pregnancy outcomes [9]. These distal risk factors may be influential in the perpetuation of poor birth outcomes among certain groups.

Ounsted and Ounsted [10] theorized that women who had constrained, *in utero* growth were more likely to have offspring with intrauterine growth retardation. Since this seminal article, several studies that examined maternal and offspring birth outcomes have been published [11–13]. Maternal BW has been consistently shown to be one of the strongest predictors of offspring BW [14]. Each 100-gram increase in maternal BW was associated with, on average, an additional 11–28 gram increase in offspring BW [15–18]; mothers who were LBW at their own birth had a two-fold increase in risk of having a LBW infant [19]. However, there is limited consensus concerning the potential nonlinear relationships of maternal and offspring BW [20,21] and whether the relationships differ for male and female offspring [22]. Despite the association of BW with adult BMI [23,24] and the importance of ppBMI on the course and outcomes of the pregnancy [25], the role of maternal

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ppBMI as moderator of maternal-offspring BW associations has also not been examined. To address these limitations, we used a well-characterized pregnancy cohort to investigate overall and sex-specific associations between maternal and offspring BW.

Materials and methods

Study setting and study population

The study was conducted among participants of the Omega study, a prospective cohort study (1996–2008) of pregnant women designed to examine risk factors for pregnancy complications and adverse outcomes [26]. Women were recruited from prenatal care clinics affiliated with Swedish Medical Center in Washington State and were eligible to enroll if they were at least 18 years of age, able to speak and read English, initiated prenatal care before 16 weeks of gestation, and planned to carry the pregnancy to term and deliver at one of the two study hospitals. A total of 4602 women were enrolled in the study and 4343 had singleton live-births. We had complete BW data (for the mother and the singleton live-born offspring) for $n = 3804$ Omega study participants. In the current analyses, we included infants with BW at least 300 grams ($n = 3800$). Participants were then excluded from analyses if they were missing data on gestational age at delivery ($n = 2$), offspring sex ($n = 3$), smoking history ($n = 4$), gestational diabetes ($n = 48$), preeclampsia ($n = 1$), or weight gain during pregnancy ($n = 8$). These were not mutually exclusive. The final sample for analyses included 3736 mother-offspring dyads. The protocol used in the Omega study was approved by the Institutional Review Boards of Swedish Medical Center and Tacoma General Hospital, and all women provided written informed consent.

Data collection

In-person interviews by trained study personnel were conducted using structured questionnaires shortly after enrollment, on average 15.6-weeks gestation (SD = 2.9 weeks). The interviews were used to collect data on socio-demographic characteristics, medical and family history of participants, including self-reported mothers' BW at their own birth in pounds and ounces, race, education, height, prepregnancy weight (immediately before the study pregnancy), age, prenatal cigarette smoking, and alcohol consumption. Pregnant women were followed until delivery. Information on infant BW in grams, gestational age at birth, offspring sex (male/female), and maternal weight within four weeks of delivery was abstracted from the hospital record after delivery, as was information on maternal health during the pregnancy and pregnancy complications.

Exposure and outcome

The primary exposure of interest was maternal BW, which was converted from pounds and ounces to grams. Maternal BW was modeled as 1) a continuous variable with each 1-unit change corresponding to a 100 gram change, 2) a linear spline with knots at 2500 grams (LBW) and 4000 grams (macrosomia), and 3) a binary variable indicating LBW status (<2500 vs. ≥2500 grams). The outcomes were offspring BW (as a continuous variable) and offspring LBW status.

Effect modifiers and covariates

Offspring sex was examined as a potential effect modifier. In secondary analyses, ppBMI was also considered as a potential effect modifier. Using World Health Organization criteria, ppBMI was calculated using weight (kg)/[height (m)]^2 and the following categories: underweight (<18.5 kg per m^2), normal weight (18.5–24.99 kg per m^2), and overweight/obese (≥25 kg per m^2). Race (white, black, Asian, or other), preterm birth (<37 and ≥ 37 weeks gestation), family history of diabetes (yes/no), smoking history (never, current, or former smoker), educational attainment (≤high school/>high school), maternal age (<25, 25-35, or >35 years), marital status (married/unmarried), parity (nulliparous/multiparous), gestational diabetes (yes/no), preeclampsia (yes/no), weight gain during pregnancy (inadequate, adequate, or excessive based on Institute of Medicine recommendations per ppBMI category) [27], and chronic hypertension (yes/no) were included as covariates in statistical analyses.

Statistical analyses

We used summary statistics, means (standard deviation) and counts (percentage) for continuous and categorical variables, respectively, to describe the study population. We examined overall maternal-offspring BW associations, fitting linear regression models to estimate beta coefficients (β) and 95% confidence intervals (CIs). Maternal BW was modeled as a continuous variable, linear spline [28], and binary variable (based on LBW status). In the first scenario, the slope estimated the average difference in mean offspring BW associated with a 100-gram increase in maternal BW. In the second scenario, the slope estimated differences in mean offspring BW per 100-gram increase in maternal BW among LBW (<2500 grams), normal BW (2500-3999 grams), and macrosomic (≥4000 grams) mothers. The statistical significance of the change in slope was determined using *P*-values of the coefficients obtained from a marginal linear spline model. We used the likelihood ratio test (LRT) to test the hypothesis that the maternal-offspring BW relationship was linear, against the alternative that it was not linear throughout the entire distribution of maternal BW. In the third scenario, we estimated the difference in mean BW of offspring delivered by LBW mothers compared with non-LBW mothers. We fit three models in these analyses: model 1 (unadjusted), model 2 (adjusted for a priori determined potential confounders and precision variables selected based on our intergenerational conceptual model: maternal race, family history of diabetes, smoking history, and educational attainment; maternal age, marital status, parity, and offspring sex), and model 3 (adjusted for model 2 variables and potential mediators of associations: ppBMI, preterm birth, chronic hypertension, and pregnancy complications: gestational diabetes and preeclampsia). We also fit logistic regression models to estimate the odds ratios (ORs) and corresponding 95% CIs of offspring LBW associated with maternal BW modeled as a continuous variable, linear spline, and binary variable, as aforementioned. We examined effect modification by offspring sex by repeating the analyses stratified by offspring sex. To test the statistical significance of the interactions, we fit models with indicators for maternal BW, offspring sex, and an interaction term between maternal BW and offspring sex. The *P*-value of the interaction term was used to determine the statistical significance of the multiplicative interaction.

In secondary analyses, we examined effect modification by ppBMI, among male and female offspring separately, by fitting the previously described models, stratified by ppBMI (normal and overweight/obese). We also fit models with indicators for maternal BW, ppBMI, and an interaction term between maternal BW and ppBMI to determine statistical significance of the multiplicative interaction. Given the small number of women who were underweight prepregnancy ($n = 161$), particularly in strata of both offspring sex and maternal BW (modeled as a linear spline or binary